## REMARKS

The Examiner has rejected claims 1 and 3-10 for obviousness-type double patenting over claims 1-24 of U.S. Patent No. 6,387,621 (the '621 patent) in view of Herrmann et al. Thus, the Examiner is suggesting that the subject matter of claims 1 and 3-10 is an obvious variant of the invention claimed in the '621 patent in view of the disclosure of Herrmann et al. The Applicant respectfully traverses the Examiner's rejection of claims 1 and 3-10 for obviousness-type double patenting. Claims 1 and 3-10 are not obvious over the '621 patent claims in view of Herrmann et al.

The claims of the present application specify at least the steps of generating a plot wherein the fluorescence values are recorded for each amplification cycle, performing a confidence band analysis on the plot to generate a positive or negative call, and if the call is positive, confirming the positive call by a melting temperature analysis.

Generally, the '621 patent claims are directed to performing a polymerase chain reaction (PCR) in which a baseline fluorescence region is established by confidence band analysis, and ascertaining whether the fluorescence value during a selected amplification cycle is outside the baseline fluorescence region. As conceded by the Examiner, the '621 patent claims do not specify "confirming the results by using a melting temperature analysis." The Examiner cites Herrmann et al. to provide the teaching of using a melting temperature analysis because the '621 patent claims lack this teaching.

There is no motivation to combine the '621 patent claims with Herrmann et al. As conceded by the Examiner, the '621 patent claims do not specify "confirming the results by using a melting temperature analysis." See page 3, lines 15-16 of the Office Action. With respect to Herrmann et al., the Examiner indicates that Herrmann et al. teaches "performing a PCR reaction followed by confirming the target using a melting temperature analysis." See page 3, lines 17-18 of the Office Action. Thus, neither the '621 patent claims nor Herrmann et al. expressly states

that the two steps of 1.) generating a positive call by confidence band analysis and 2.) using melting temperature analysis as a second confirmation step should be combined.

The Examiner cites *Ruiz v. A.B. Chance Company* (Fed. Cir. 2004) in which the court stated that an "an examiner may find a motivation to combine prior art references in the nature of the problem to be solved." The Examiner relies on *Ruiz* as a basis for the argument that there is motivation to combine the '621 patent claims and Herrmann et al. because, according to the Examiner, there are express statements in the '621 patent and in Herrmann et al. that suggest that Herrmann et al. solves the problem recognized in the '621 patent.

Thus, the Examiner states that the "nature of the recognized problem in U.S. Patent No. 6,387,621 lends itself to solution by combination with the Hermann reference." See page 11, lines 16-18 of the Office Action. To support his motivation to combine arguments, the statements that the Examiner points to in Herrmann et al. are that "[t]he ability to multiplex PCR analysis by color and $T_m$ has many uses in addition to multiplex genotyping. For example, internal amplification controls are often needed for infectious disease and translocation testing to verify that amplifiable DNA or cDNA is present even if the target amplification is negative. Another common need is for multiplexing a competitor as an internal standard for PCR quantification (see page 428, column 1)." See page 4, lines 14-19 of the Office Action.

To support his motivation to combine arguments, the statements that the Examiner points to in the '621 patent are that "accurately discriminating between positive and negative samples is not easy in practice (see column 6, lines 15-16)," and that "[a]utomatic identification of the background is surprisingly difficult. (see column 6, lines 48-49)." See page 5, lines 3-6 of the office action. The Examiner argues that Herrmann et al. provides an additional solution for the problem recognized in the '621 patent that accurately discriminating between positive and negative PCR samples is difficult.

The Examiner indicates that the statements discussed above provide motivation to a skilled artisan to combine Herrmann et al. with the '621 patent claims because the '621 patent indicates that accurately discriminating between positive and negative samples is difficult, and

Herrmann et al. provides a solution to this problem by "providing a means to accurately discriminate between positive and negative PCR samples." See page 5, lines 7-8 of the Office Action.

First, the statements in the '621 patent that "accurately discriminating between positive and negative samples is not easy in practice," and that "[a]utomatic identification of the background is surprisingly difficult" do not, *when taken in the context of the '621 patent*, motivate a skilled artisan to combine the invention of the '621 patent claims with Herrmann et al. or with any other reference that describes confirmatory methods for identifying PCR amplification products. The '621 patent has provided a solution to the problem that "accurately discriminating between positive and negative samples is not easy in practice." The solution to this problem that is provided by the '621 patent is confidence band analysis to generate a positive or negative call. There is no suggestion in the '621 patent that any additional confirmatory method, in addition to confidence band analysis, is needed to discriminate between positive and negative PCR samples.

The statements in the '621 patent that the Examiner points to that "accurately discriminating between positive and negative samples is not easy in practice," and that "[a]utomatic identification of the background is surprisingly difficult" are found in column 6, lines 15-17 and column 6, lines 48-49 of the '621 patent. These statements are made in a section of the '621 patent that discusses problems with prior art methods that had previously been used to attempt to discriminate between positive and negative PCR samples. These statements are in a section of the '621 patent that leads into the specific description in the '621 patent of the steps that are performed to carry out confidence band analysis according to the method described in the '621 patent. This specific description of the steps in the confidence band analysis method described in the '621 patent begins at column 6, line 55 and continues through column 8, line 67. The last statements in this section of the '621 patent are that "[i]f the test point fluorescence is outside of the confidence interval, the sample is positive. If it is within the interval, the sample is

negative. FIGS. 7 and 8 are samples which are positive, while FIGS. 9-11 are negative samples." See column 8, lines 64 to 67 of the '621 patent.

There is no suggestion in the '621 patent that the confidence band analysis method described in the '621 patent has not solved the problem addressed in the '621 patent or that any additional verification or confirmatory method is needed. In fact, the last statements, prior to the '621 patent claims, describing the specific steps of the confidence band analysis method that is the subject of the '621 patent are that "[i]f the test point fluorescence is outside of the confidence interval, *the sample is positive*. If it is within the interval, *the sample is negative*." See column 8, lines 64 to 66 of the '621 patent. (Emphasis added). These statements provide no indication that the results of the confidence band analysis method described in the '621 patent could be inaccurate in any way or that any additional verification or confirmatory method is needed. To the contrary, the statements that if a fluorescence value is outside of the confidence band interval, *the sample is positive*, and if the value is within the confidence band interval, *the sample is negative*, indicate that the results of the confidence band analysis method described in the '621 patent are conclusive.

The Examiner has taken the statements in the '621 patent that "accurately discriminating between positive and negative samples is not easy in practice," and that "[a]utomatic identification of the background is surprisingly difficult" out of the context in which those statements are made in the '621 patent. These statements are made in a section of the '621 patent that discusses the problem that is addressed in the '621 patent, but that is resolved by the confidence band analysis method described in the '621 patent. The confidence band analysis method described in the '621 patent is the solution to the problem that "accurately discriminating between positive and negative samples is not easy in practice."

There is no suggestion in the '621 patent that the confidence band analysis method described in the '621 patent has not solved the problem pointed to by the statements that "accurately discriminating between positive and negative samples is not easy in practice," and that "[a]utomatic identification of the background is surprisingly difficult." There is simply no

statement in the '621 patent that definitively suggests that the confidence band analysis method described in the '621 patent has not solved the problem addressed in the '621 patent and the Examiner has not pointed to such a statement. Indeed, Applicant respectfully submits that the only suggestion that an additional confirmatory method is needed to verify the results obtained by confidence band analysis is the Examiner's hindsight through the lens of Applicant's own disclosure in the present application, and such hindsight analysis is not allowed. The '621 patent is devoid of any suggestion that an additional confirmatory method is needed to verify the results obtained by confidence band analysis. It is Applicant's own disclosure in the present application that first suggests that an additional confirmatory method (*i.e.*, melting temperature analysis) may be needed to verify the results obtained by confidence band analysis.

Furthermore, even if the '621 patent suggested that confidence band analysis does not solve the problem described in the '621 patent, and, again Applicant contends that there is simply no such suggestion in the '621 patent, the nature of the problem pointed to in the '621 patent would not lead a skilled artisan to look to Herrmann et al. for a solution. The '621 patent describes a method for accurately discriminating between *positive and negative samples* based on an analysis of the background fluorescence during a PCR reaction. Herrmann et al. has nothing to do with analyzing background fluorescence to discriminate between *positive and negative PCR samples*, but, rather involves differentiating between multiple DNA's in a sample.

Thus, accurate discrimination between positive and negative samples in the context of the '621 patent is accomplished without analysis or comparison to different signals resulting from different nucleic acids in the sample. In contrast, melting temperature analysis in the context of Herrmann et al. is used to determine the presence of a nucleic acid in a sample by analyzing and comparing different signals resulting from different nucleic acids in the sample.

In fact, Herrmann et al. is limited to the use of melting curve analysis in the context of discriminating between multiple DNA's (*i.e.*, multiple signals) in a PCR sample. Herrmann et al. solves a completely different problem than is pointed to in the '621 patent. In this regard, the statements cited by the Examiner in Herrmann et al. that the Examiner argues

provide express motivation to combine Herrmann et al. with the '621 patent by providing a solution to the problem identified in the '621 patent are all directed to using melting temperature analysis to discriminate between multiple DNA's in a PCR sample.

The statements cited by the Examiner in Herrmann et al. are directed to discrimination between multiple DNA's 1.) in the context of multiplex genotyping, 2.) in the context of discrimination between an internal amplification control and the target DNA, and 3.) in the context of discrimination between a competitor as an internal standard and the target DNA. These statements in Herrmann et al. are unambiguously limited to the use of melting curve analysis in the context of multiplex experiments. In other words, Herrmann et al. is unambiguously limited to the use of melting temperature analysis to discriminate between multiple DNA's in a PCR sample. The methods described in Herrmann et al. have nothing to do with analyzing background fluorescence to discriminate between positive and negative PCR samples. Thus, the nature of the problem pointed to in the '621 patent would not lead a skilled artisan to look to Herrmann et al. for a solution, and there is no motivation to combine these references.

The Examiner cites additional statements in the '621 patent and in Herrmann et al. to support his argument that the nature of the problem pointed to in the '621 patent would lead a skilled artisan to look to Herrmann et al. for a solution, and further that statements in Herrmann et al. would lead to the combination of Herrmann et al. with the '621 patent. The Examiner states on page 10, lines 3-6 of the office action that Herrmann et al. teaches that a single nucleic acid could be analyzed using the method described in Herrmann et al. because Herrmann et al. states that "Probes of a single color are usually used for genotyping" (see page 425, line 6 of Herrmann et al.).

Again, the Examiner has taken a statement out of the context in which it is made in the reference. The statement that immediately follows the statement referred to by the Examiner on page 425, line 6 of Herrmann et al. is that "[f]our alleles at two different loci have been genotyped by multiplexing probe $T_m$s of a single color." Thus, in the proper context

Herrmann et al. states that "Probes of a single color are usually used for genotyping. Four alleles at two different loci have been genotyped by multiplexing probe $T_m$s of a single color." These statements together indicate that probes of a single color have been used to identify four different alleles by multiplex genotyping which again refers to discriminating between multiple DNA's in a sample as discussed above. Thus, the statement that "[p]robes of a single color are usually used for genotyping" does not at all teach that a single nucleic acid could be analyzed by the method described in Herrmann et al. as the Examiner contends.

Furthermore, the Examiner cites an additional statement in the '621 patent to support an argument that the nature of the problem pointed to in the '621 patent would lead a skilled artisan to look to Herrmann et al. for a solution. The Examiner indicates on page 10, lines 6-13 of the office action that claim 11 of the '621 patent teaches allele comparisons. However, claim 11 specifies a method where the nucleic acid is further analyzed to determine the presence of "a particular allele." Claim 11 provides no indication that multiple alleles are compared and the '621 patent specification provides no indication that the method of claim 9 or claim 11 is used for multiplex genotyping. Thus, claim 11 of the '621 patent teaches single allele identification and does not teach multiple allele comparisons as contended by the Examiner.

As discussed above, the Examiner has taken the statements in the '621 patent that "accurately discriminating between positive and negative samples is not easy in practice," and that "[a]utomatic identification of the background is surprisingly difficult" out of the context in which those statements are made in the '621 patent to support his argument that the '621 patent suggests that confirmatory methods in addition to confidence band analysis are needed to accurately discriminate between positive and negative PCR samples. Again, there is simply no statement in the '621 patent that suggests that the confidence band analysis method that is the subject of the '621 patent has not solved the problem described in the '621 patent and the Examiner has not pointed to such a statement. The only suggestion that a confirmatory method in addition to confidence band analysis may be needed to accurately discriminate between positive and negative PCR samples is through the Examiner's hindsight based on review of

Applicant's present application, and such hindsight analysis is improper.

Moreover, the nature of the problem pointed to in the '621 patent would not lead a skilled artisan to look to Herrmann et al. for a solution because the methods described in Herrmann et al. have nothing to do with discriminating between positive and negative PCR samples based on analysis of background fluorescence, and this is the problem described in the '621 patent. Accordingly, there is no motivation to combine the '621 patent and Herrmann et al. either based on express statements in the '621 patent or in Herrmann et al. or based on the nature of the problem to be solved, and the Applicant's claimed method is not obvious over the '621 patent claims in view of Herrmann et al. Withdrawal of the rejection of claims 1 and 3-10 for obviousness-type double patenting is respectfully requested.

The Examiner also rejected claims 1 and 3-10 under 35 U.S.C. § 103(a) over Wittwer in view of Hermann et al. Wittwer is the European counterpart of the '621 patent. The Examiner made the same substantive arguments for rejecting claims 1 and 3-10 under 35 U.S.C. § 103(a) based on Wittwer in view of Herrmann et al. as the Examiner made for rejecting claims 1 and 3-10 for obviousness-type double patenting. Accordingly, the Applicant's arguments made with respect to the obviousness-type double patenting rejection apply with equal force to this rejection except that the text of Wittwer is applicable rather than the claims of the '621 patent. Withdrawal of the rejection of claims 1 and 3-10 under 35 U.S.C. § 103(a) over Wittwer in view of Hermann et al. is respectfully requested.

## CONCLUSION

The foregoing remarks are believed to fully respond to the Examiner's rejections. The claims are in condition for allowance. Applicant respectfully requests allowance of the claims, and passage of the application to issuance.

Respectfully submitted,

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